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Kabachnik-Fields Reaction by Mechanochemistry: New Horizons from Old Methods

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Kabachnik-Fields Reaction by Mechanochemistry: New Horizons from Old Methods / Fiore C.; Sovic I.; Lukin S.; Halasz I.; Martina K.; Delogu F.; Ricci P.C.; Porcheddu A.; Shemchuk O.; Braga D.; Pirat J.-L.; Virieux D.; Colacino E.. - In: ACS SUSTAINABLE CHEMISTRY & ENGINEERING. - ISSN 2168-0485. - ELETTRONICO. - 8:51(2020), pp. 18889-18902. [10.1021/acssuschemeng.0c05744]

*Availability:*

This version is available at: <https://hdl.handle.net/11585/792793> since: 2021-01-29

*Published:*

DOI: <http://doi.org/10.1021/acssuschemeng.0c05744>

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# Kabachnik–Fields Reaction by Mechanochemistry: New Horizons from Old Methods

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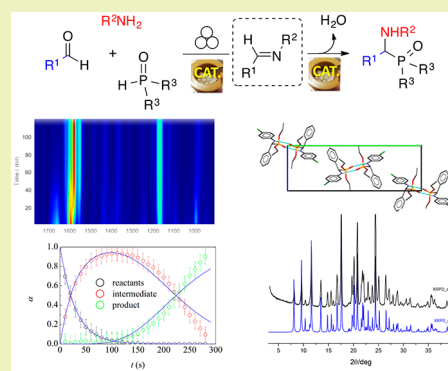


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**ABSTRACT:**  $\alpha$ -Aminophosphonates are an important class of biologically active compounds, attracting considerable attention in medicinal chemistry, by inhibiting enzymes involved in amino acid metabolism. Herein, the Kabachnik–Fields domino reaction was investigated by mechanochemistry for the first-time preparation of  $\alpha$ -aminophosphonate derivatives in high yields and with full selectivity, outperforming comparable solution procedures. The reaction occurs without the addition of any external catalyst, possibly via a metal-mediated process occurring on the surface of the jar (zirconium oxide was used as the milling media). The mechanism of the mechanochemical reaction was also investigated by *in situ* Raman spectroscopy, and the kinetic behavior was disclosed. The solid-state structures of two representative compounds have been determined by single-crystal X-ray diffraction.



**KEYWORDS:**  $\alpha$ -Aminophosphonates, Domino reactions, Kabachnik–Fields reaction, Mechanochemistry, Raman *in situ* monitoring, Kinetics, Solid-state characterization

## INTRODUCTION

One-pot synthetic strategies such as tandem, domino, or cascade<sup>1,2</sup> and multicomponent reactions<sup>3</sup> have been recognized as processes with minimal waste generation. These synthetic strategies *benign by design* are usually characterized by high atom economy and avoid the isolation of the reaction intermediates and synthetic pathways involving protection/deprotection steps. In combination with enabling technologies,<sup>4</sup> they become powerful tools to address the quest of sustainable organic synthesis.<sup>5</sup> In this regard, mechanochemistry<sup>6–9</sup> plays a central role, by improving the efficiency of a process and its ecological footprint.

One of us previously reported the mechanochemical preparation of N- and C-functionalized amino acid derivatives<sup>10,11</sup> and used them as building blocks to access biologically active compounds<sup>12–15</sup> and highly relevant active pharmaceutical ingredients<sup>16</sup> (API). Wishing to broaden the knowledge in this area of investigation, we turned our attention to the mechanochemical preparation of  $\alpha$ -aminophosphonic acids and their corresponding esters,<sup>17,18</sup> which are structural P-analogues of  $\alpha$ -amino acids.

They present an amino phosphonate framework P(O)–C–N and are biosisters of the carboxyl unit<sup>19</sup> (Scheme 1).

Indeed, the tetrahedral structure of the phosphonyl group acts as stable mimics of the *tetrahedral carbon intermediate* (synthetic equivalent of *transition state analogue*),<sup>20</sup> inhibiting

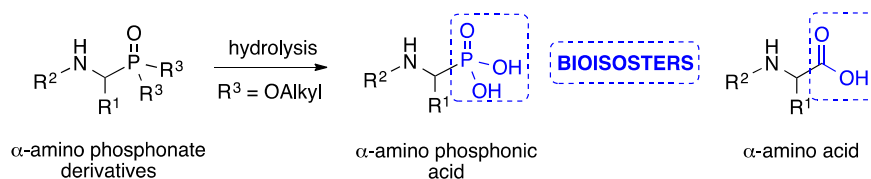
enzymes or receptors to which natural amino acids normally bind.<sup>21</sup> As a consequence, this family of compounds displays diverse biological activities, raising growing interest in medicinal and pharmaceutical science applications.<sup>22</sup>

A unique method to build the amino phosphonate framework P(O)–C–N<sup>22–27</sup> relies on the three-component domino Kabachnik–Fields reaction (KF-3CR).<sup>28–30</sup> Also referred to as phospho-Mannich, the reaction involves a hydrophosphoryl compound (e.g., dialkyl phosphite or secondary phosphine oxide), a carbonyl compound (aldehyde or ketone), and a primary or a secondary amine, resulting in the formation of  $\alpha$ -aminophosphonates ( $R^3 = \text{OAlkyl}$ ) or  $\alpha$ -aminophosphine oxides ( $R^3 = \text{Ph}$ ) (method A, Scheme 2).

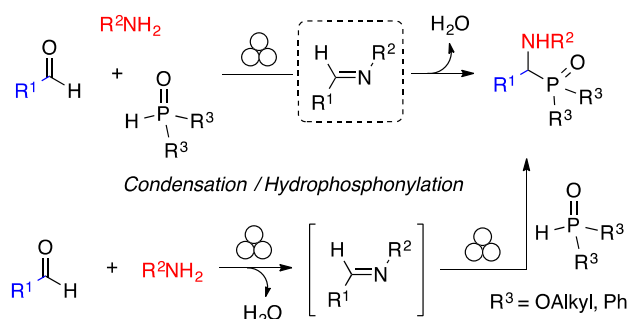
The reaction is really attractive and presents several advantages: (a) the cheapness and availability of reactants, (b) its broad scope enabling the introduction of *all-in-one* C-, N-, and P-modifications on the  $\alpha$ -amino phosphonate backbone, (c) its importance from the point of view of

Received: August 5, 2020

Revised: November 4, 2020

Scheme 1. Bioisosterism of  $\alpha$ -Aminophosphonate DerivativesScheme 2. General Approaches for the Preparation of  $\alpha$ -Aminophosphonic Esters and  $\alpha$ -Aminophosphine Oxides<sup>a</sup>

Method A : Kabachnik-Fields reaction - (Domino process)



Method B : Pudovik reaction - (two-step sequence)

<sup>a</sup>The mechanochemical activation<sup>31</sup> is also included here as an alternative to solution-based procedures.

sustainability, intrinsically displaying high atom economy, and (d) straightforward access to biologically relevant compounds.

In solution, the KF-3CR is flanked by an alternative synthetic pathway where the three-component domino reaction is divided into two distinct steps (Pudovik reaction)<sup>32</sup> involving the formation of the intermediate Schiff base (*step 1*) followed by the addition of the “P-nucleophile” to the C=N bond (*step 2*) (method B, Scheme 2).

However, the outcome of the reaction occurring via these two different synthetic pathways is strongly influenced by the nature of the substrates and the solvent used.

Novel reaction conditions based on activation by alternative energy inputs in “batches” (microwaves,<sup>21,33</sup> ultrasounds<sup>34</sup>) or under continuous flow,<sup>35,36</sup> with sustainable solvents<sup>37</sup> or solvent-free<sup>24</sup> (including manual grinding in a mortar),<sup>38</sup> catalyzed or not, were explored to improve the selectivity, reaction efficiency, and environmental footprint of KF-3CR compared to the conventional methods in solution.<sup>17,24,26</sup>

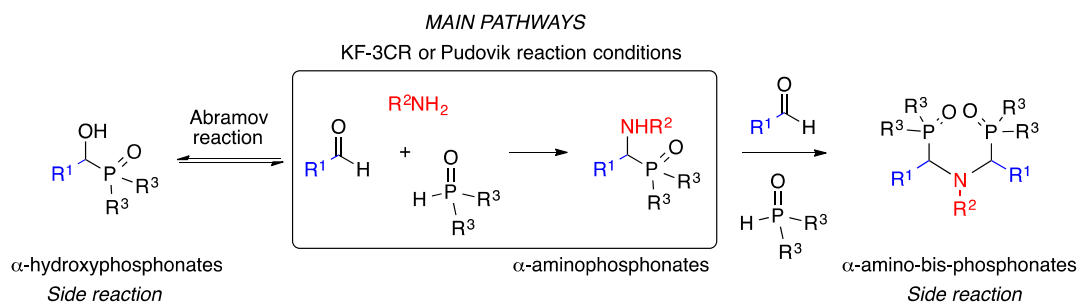
To our surprise, no reports deal with the use of ball-milling processes for the preparation of  $\alpha$ -aminophosphonic acid derivatives and more generally for the formation of C(sp<sup>3</sup>)–

Table 1. Selected Data for the Screening of the Reaction and Milling Conditions for the Preparation of  $\alpha$ -Aminophosphonates 1 and 2<sup>a</sup>

**Method A**

entry	R <sup>2</sup> <sub>(a,b)</sub> NH <sub>2</sub>	H(O)P(OEt) <sub>2</sub> (equiv)	LAG	jar/ball <sup>a</sup> no.	t (h)/rpm	conv (%)	product/yield (%)
1a	R <sup>2</sup> <sub>a</sub>	1.0		SS <sup>a</sup> /25	4 <sup>b</sup> /450	100	E-1 <sup>c</sup> /99
1b	R <sup>2</sup> <sub>b</sub>	1.0		SS <sup>a</sup> /25	4 <sup>b</sup> /450	100	E-2 <sup>c</sup> /98
2a	R <sup>2</sup> <sub>a</sub>	1.0		ZrO <sub>2</sub> /25	4 <sup>b</sup> /450	73 <sup>d</sup>	1/ni <sup>e</sup>
2b	R <sup>2</sup> <sub>b</sub>	1.0		ZrO <sub>2</sub> /25	4 <sup>b</sup> /450	35 <sup>d</sup>	2/ni <sup>e</sup>
3a	R <sup>2</sup> <sub>a</sub>	1.0	EtOH <sup>f</sup>	ZrO <sub>2</sub> /50	6/600	71 <sup>d</sup>	1/ni <sup>e</sup>
3b	R <sup>2</sup> <sub>b</sub>	1.0	EtOH <sup>f</sup>	ZrO <sub>2</sub> /50	6/600	66 <sup>d</sup>	2/ni <sup>e</sup>
4a	R <sup>2</sup> <sub>a</sub>	1.5		ZrO <sub>2</sub> /50	6/600	100	1/98
4b	R <sup>2</sup> <sub>b</sub>	1.5		ZrO <sub>2</sub> /50	6/600	100	2/98

<sup>a</sup>(Fritsch Pulverisette 7 Classic Line. Image reproduced by kind permission from Fritsch France.) Reaction scale: 1.5 mmol in 12 mL jar, SS = stainless steel, ball no. = number of 5 mm  $\varnothing$  balls. <sup>b</sup>Cycled milling (2 cycles of 2 h each) with *ex situ* analyses in between. <sup>c</sup>Only the *E*-isomer is formed. The *E*-geometry was assigned on the basis of previous reports for H<sup>A</sup>C=N proton: for *E*-1<sup>45</sup>  $\delta$  (ppm): 8.44 ppm, for *E*-2<sup>46,47</sup>  $\delta$  (ppm): 8.60 ppm. <sup>d</sup>The conversion was determined by comparing the <sup>1</sup>H NMR area of residual H<sup>A</sup>C=N proton of the Schiff base to the area of the P-CH<sup>A</sup> proton in the final compound. <sup>e</sup>ni = not isolated (some reactants and/or imine were still present in the crude). <sup>f</sup>Liquid assisted grinding conditions (LAG) using EtOH (100  $\mu$ L,  $\eta = 0.17$ ), with  $\eta$  value<sup>44</sup> defined as the volume of the solvent (in  $\mu$ L)/the sample weight (in mg).

Scheme 3. Main Side Reactions Occurring during the Preparation of  $\alpha$ -Aminophosphonates<sup>17,53</sup>

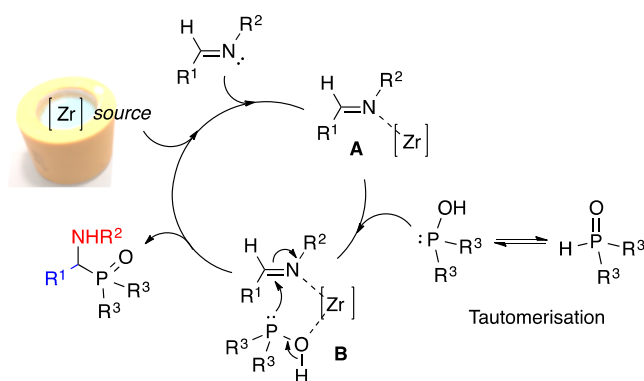
phosphorus bonds, while only one account describes the metal-catalyzed C(sp<sup>2</sup>)-phosphorus bond formation in a ball-mill.<sup>39</sup>

By virtue of the high synthetic potential displayed by the KF-3CR, the activation by ball-milling becomes particularly appealing. We report herein the unprecedented mechanochemical preparation of several new  $\alpha$ -aminophosphonate derivatives accessed straightforwardly, selectively, and in very high yields. The use of any organic solvent (including during the workup) or added catalyst was avoided, and there was no need for postreaction treatments. For the first time, the mechanism of the mechanochemically activated KF-3CR was disclosed by *in situ* monitoring by Raman spectroscopy<sup>40,41</sup> and kinetic features of the mechanochemical process were examined by a mathematical model, allowing the description of the chemical changes under mechanical stress.<sup>42,43</sup> To complete the study, the solid-state characterization of two representative compounds was carried out also in order to compare the structural and crystal packing features of the compounds obtained mechanochemically with those of analogous compounds obtained by conventional solution methods.

## RESULTS AND DISCUSSION

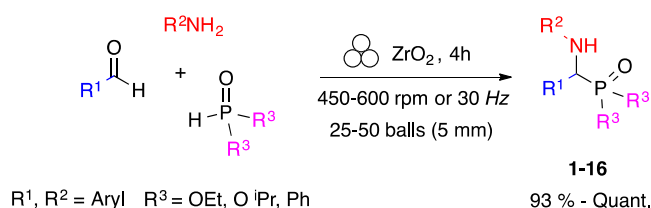
**Optimization of Reaction Conditions.** The mechanochemical preparation of  $\alpha$ -aminophosphonates ( $R^3 = \text{OAlkyl}$ )

### Scheme 4. Plausible Mechanism for the Hypothesized Zr-Catalyzed Synthesis of $\alpha$ -Aminophosphonates by Mechanochemistry



and  $\alpha$ -aminophosphine oxides ( $R^3 = \text{Ph}$ ) was investigated according the two main pathways mentioned above: the Kabachnik–Fields reaction<sup>28,29</sup> (method A) and its one-pot/two-step modification, known as the Pudovik reaction<sup>32</sup> (method B) (Scheme 2).

### Scheme 5. Library of $\alpha$ -Aminophosphonate Derivatives Prepared by Ball-Milling



**Table 2. Investigation of the Selectivity for Mechanochemical KF-3CR with Cyclohexylamine**

entry	method	$R^1\text{CHO}$	$R^2\text{NH}_2$	$\alpha\text{-OH}/\alpha\text{-NH}_2$ (%) <sup>a,b</sup>	<sup>31</sup> P NMR $\delta$ (ppm) <sup>c</sup>	
					$\alpha\text{-OH}$	$\alpha\text{-NH}_2$
1	A	Ph-	C <sub>6</sub> H <sub>11</sub> -	60/40	21.3 <sup>72</sup>	24.2 <sup>73</sup>
2	B	Ph-	C <sub>6</sub> H <sub>11</sub> -	64/36	21.3 <sup>72</sup>	24.2 <sup>73</sup>
3	A	4-NO <sub>2</sub> - C <sub>6</sub> H <sub>4</sub> -	C <sub>6</sub> H <sub>11</sub> -	27/63	19.9 <sup>d,72</sup>	24.9 <sup>d</sup>
4	A	4-Cl- C <sub>6</sub> H <sub>4</sub> -	C <sub>6</sub> H <sub>11</sub> -	41/59	20.7 <sup>72,74</sup>	23.6 <sup>75</sup>

<sup>a</sup> $\alpha\text{-OH}$  =  $\alpha$ -hydroxyphosphonate,  $\alpha\text{-NH}_2$  =  $\alpha$ -aminophosphonate.

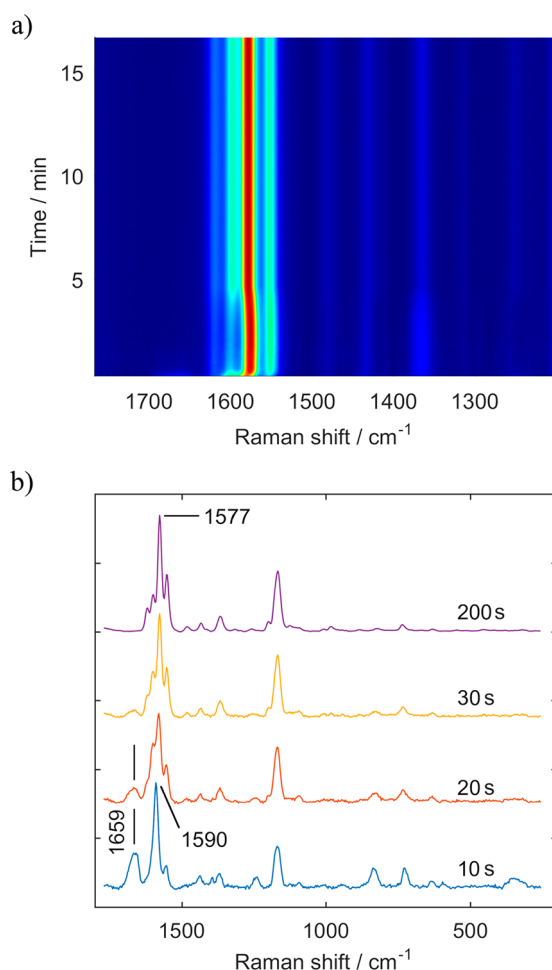
<sup>b</sup>The ratio was determined by <sup>1</sup>H NMR and <sup>31</sup>P NMR of the crude.

<sup>c</sup>CDCl<sub>3</sub> was used. <sup>d</sup>The value was attributed by comparing the chemical shift with that one reported for diethyl [hydroxy(4-nitrophenyl)methyl]phosphonate: <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  (ppm) 19.9.<sup>72</sup>

To optimize the reaction conditions and the mechanochemical parameters, two benchmark reactions, run in parallel in a planetary ball-mill, were selected. Two different amines (*p*-chloro aniline and 2-naphthylamine) were reacted with benzaldehyde and diethyl phosphite ( $R^3 = \text{OEt}$ ), and a selection of data is reported in Table 1.

Parameters such as rotation frequency (up to 800 rpm), milling time, the material of the jars and balls (stainless steel or zirconium oxide), number of milling balls (25 or 50), mode of operation (cycled or continuous), in neat conditions, or using liquid-assisted grinding<sup>44</sup> (LAG) procedures were investigated together with the relative stoichiometry of the reactants.

The first trials were performed in a 12 mL stainless steel jar with 25 balls (5 mm diameter, total weight  $m^{\text{tot}} = 12.7$  g) milling a stoichiometric amount of the reactants at 450 rpm during cycled milling (Table 1, entries 1a and 1b). Monitoring the reaction by both <sup>1</sup>H NMR and <sup>31</sup>P NMR revealed that the conversion was not complete after the first milling cycle (2 h), with 33% of residual aldehyde still present in the crude, together with the corresponding *E*-imines. Even by extending the milling time for a further 2 h, the corresponding  $\alpha$ -

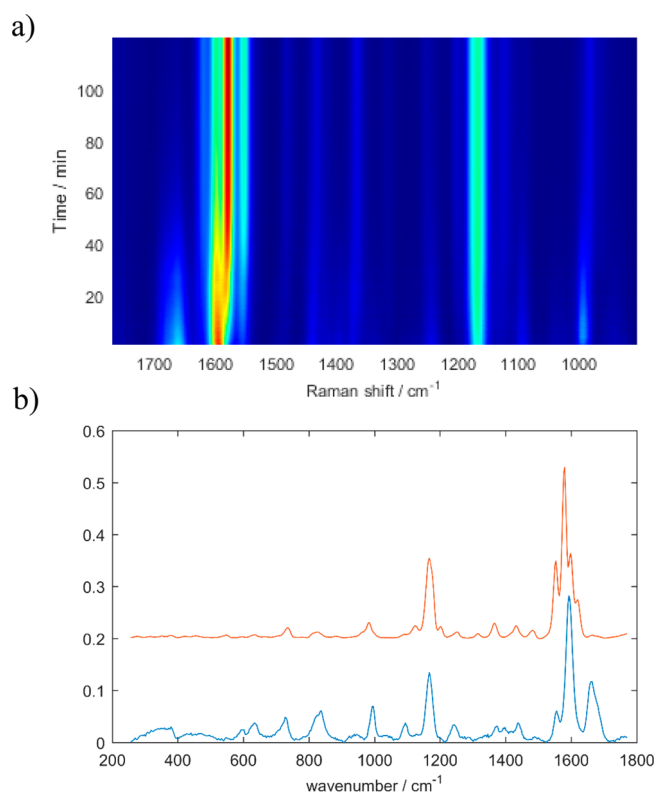


**Figure 1.** (a) 2D plot of milling experiment for the formation of  $\alpha$ -aminophosphonate **9** in the presence of NaCl. (b) Normalized Raman spectra after 10, 20, 30, and 200 s.

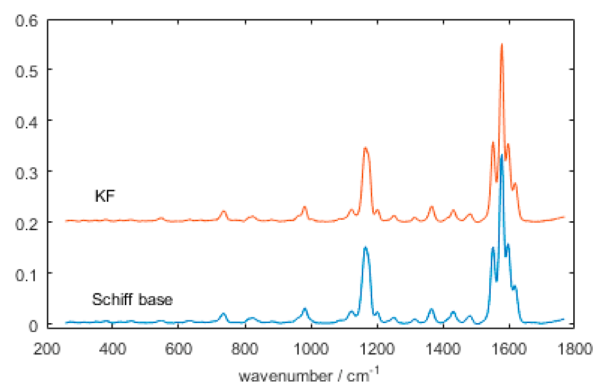
aminophosphonic acid diethyl esters **1** and **2** were not formed even in trace amounts.

However,  $^{31}\text{P}$  NMR analyses of the crude mixtures after 4 h milling indicated the presence of unreacted diethyl phosphite [ $\delta$  (ppm): 7.34 ppm in  $\text{CDCl}_3$ ] while  $^1\text{H}$  NMR spectra clearly showed the full conversion of benzaldehyde and the amine, in favor of the selective and almost quantitative formation of the corresponding *E*-imines *E*-1<sup>45</sup> and *E*-2<sup>46,47</sup> (Table 1, entries 1a and 1b respectively). The recovery of pure solid *E*-imines *E*-1 and *E*-2 was straightforward: water was added directly into the jar, followed by the filtration of the precipitate and drying *under vacuo* over  $\text{MgSO}_4$ , while the unreacted liquid diethyl phosphite and/or its hydrolyzed counterpart were easily eliminated in the water phase.

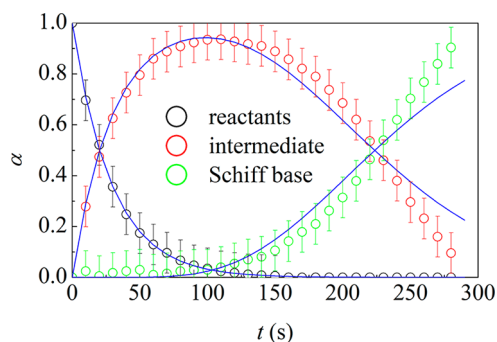
Speculating that the jar material could somehow influence the mechanochemical reactivity of the system<sup>48–52</sup> by promoting the addition of the P-nucleophile to the  $\text{C}=\text{N}$  bond, further tests were performed (entries 2–4). While keeping the same chemical, technological, and process parameters, zirconium oxide jars and balls (5 mm diameter, total weight  $m^{\text{tot}} = 10.2$  g) were used instead of stainless steel grinding jars. In this case, even if the kinetic energy delivered to the system was lower ( $m^{\text{tot}} = 10.2$  g for  $\text{ZrO}_2$  vs  $m^{\text{tot}} = 12.7$  g for stainless steel, 5 mm diameter balls), and full conversion of the reactants could not be achieved. The addition of diethyl phosphite to the  $\text{C}=\text{N}$  bond of the transient imine took place,



**Figure 2.** (a) 2D plot milling of dmab and pClan in the presence of  $\text{Na}_2\text{SO}_4$ . (b) Normalized Raman spectra after 20 s and 2 h of milling.

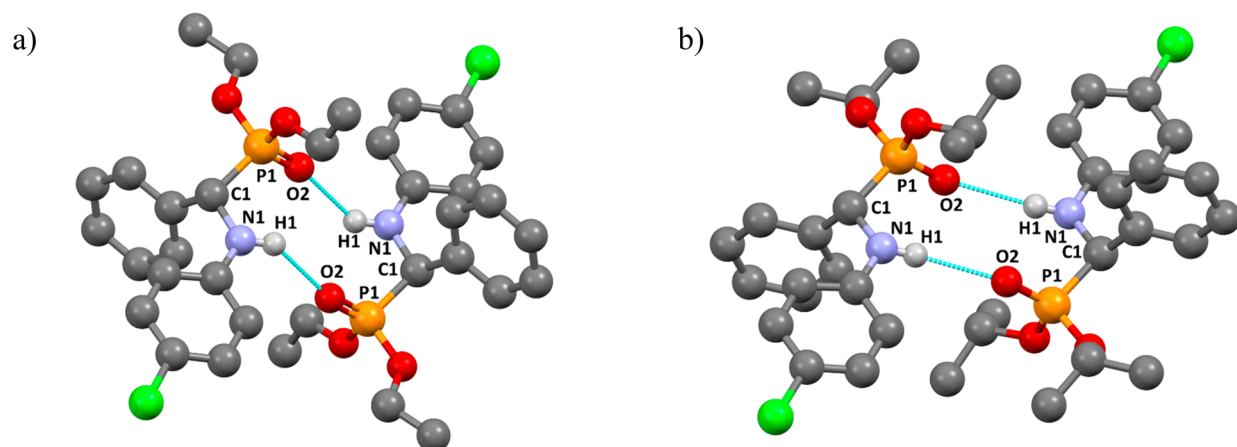


**Figure 3.** Comparison of final Raman spectra for the KF-3CR (orange line) and the corresponding Schiff base prepared separately upon milling of dmab and pClan (blue line).



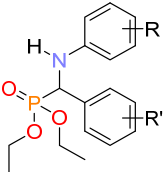
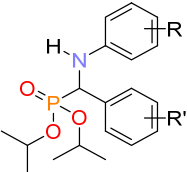
**Figure 4.** Reaction profile for Schiff base formation in the KF-3CR reaction leading to the  $\alpha$ -aminophosphonate **9**. Best-fit kinetic curves are shown.





**Figure 5.** Molecular structures of **1** (a) and **11** (b) showing the labeling schemes of aminophosphonate groups and the hydrogen bonded rings formed by pairs of molecules in the crystals. H<sub>CH</sub> hydrogen atoms omitted for clarity.

**Table 3.** Comparison of Hydrogen Bonded Dimers N<sub>NH</sub>⋯O<sub>PO</sub> Distance of Diethyl and Diisopropyl Aminophosphonates

		
<b>CSD Refcode –</b>	DEABPH <sup>78</sup> – 2.957	RAFFAH <sup>79</sup> – 3.070
<b>N<sub>NH</sub>⋯O<sub>PO</sub> bond length, Å</b>	LUPHAG <sup>80</sup> – 2.958	XUXJAC <sup>81</sup> – 3.079
	PESKAC <sup>82</sup> – 2.904	XUXJEG <sup>81</sup> – 3.066

leading to the corresponding  $\alpha$ -aminophosphonic acid diethyl esters **1** and **2** (entry 2).

Further on, the mechanical energy transferred to the mixture was tuned by applying different combinations of rotation speed/number of balls, while the reaction conditions were adjusted by increasing the relative stoichiometry of diethyl phosphite (entries 3 and 4). Indeed, when using a stoichiometric amount of the reactants, full conversion was usually not achieved (entries 2 and 3). This was probably due to the partial hydrolysis of the diethyl phosphite in the presence of water<sup>28</sup> generated *in situ* during the condensation step leading to the intermediate imine.

Better results were obtained with a continuous milling mode in zirconium oxide jars (at 600 rpm for 6 h), doubling the number of balls with (50 balls,  $m^{\text{tot}} = 20.5$  g) and using 1.5 equiv of diethyl phosphite (entry 4). As per the imines *E-1* and *E-2*, also  $\alpha$ -aminophosphonates **1** and **2** were recovered pure and in high 98% yield by simply adding water to the crude mixture and applying the same workup procedures described so far. With the exception of water, generated during the condensation step, no other byproducts were formed and the precipitation/filtration workup allowed the elimination of residual diethyl phosphite derivatives.

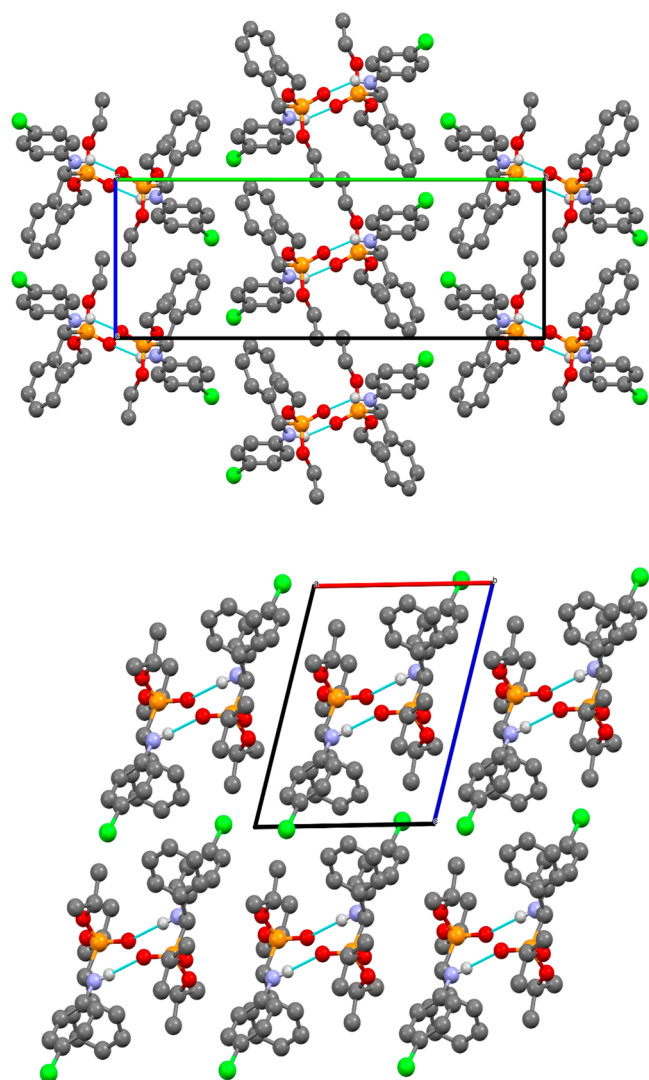
Similar conversions and yields were obtained by increasing the milling speed up to 800 rpm for a shorter reaction time (4 h milling, under continuous milling mode), while LAG conditions with EtOH (entry 3) were detrimental. <sup>1</sup>H NMR, <sup>31</sup>P NMR, and GC-MS analyses of the crude showed the

presence of  $\alpha$ -hydroxyphosphonate byproducts,<sup>17,53</sup> due to the competitive Abramov addition<sup>54</sup> of the P-nucleophile directly to the C=O carbonyl bond of the starting aldehyde (Scheme 3).

These results showed that the hardness and density of the material could influence the activation process possibly via surface-mediated phenomena involving the jar material (and the reactants), by promoting the addition of diethyl phosphite to the C=N bond of the transient imine (Scheme 4).

It is known that in solution, Lewis acids are effective catalysts for the Pudovik reaction, promoting the nucleophilic addition of phosphites to imines.<sup>55,56</sup> The preparation of  $\alpha$ -aminophosphonates was also described in the presence of Zr-based catalysts at room temperature: in solution (e.g. with ZrCl<sub>4</sub>),<sup>57</sup> solvent-free [e.g. with Cp<sub>2</sub>Zr(OSO<sub>2</sub>C<sub>4</sub>F<sub>9</sub>)<sub>2</sub>·2H<sub>2</sub>O,<sup>58</sup> ZrOCl<sub>2</sub>·8H<sub>2</sub>O, or ZrO(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O<sup>59</sup>] or by grinding over Zr-supported pillared clay.<sup>38</sup>

Based on all these findings, zirconium oxide jars (and balls) may play a double role, possibly acting at the same time as a *Zr source* equivalent and Lewis catalyst: (a) by generating *in situ* a more electrophilic C=N bond leading to an activated intermediate **A** by coordination between the nitrogen atom of the imine with the *Zr source* equivalent and (b) by exerting a template effect placing close together the diethyl phosphite and the activated imine **A** (intermediate **B**), thus facilitating the addition reaction yielding to  $\alpha$ -aminophosphonate (Scheme 4).



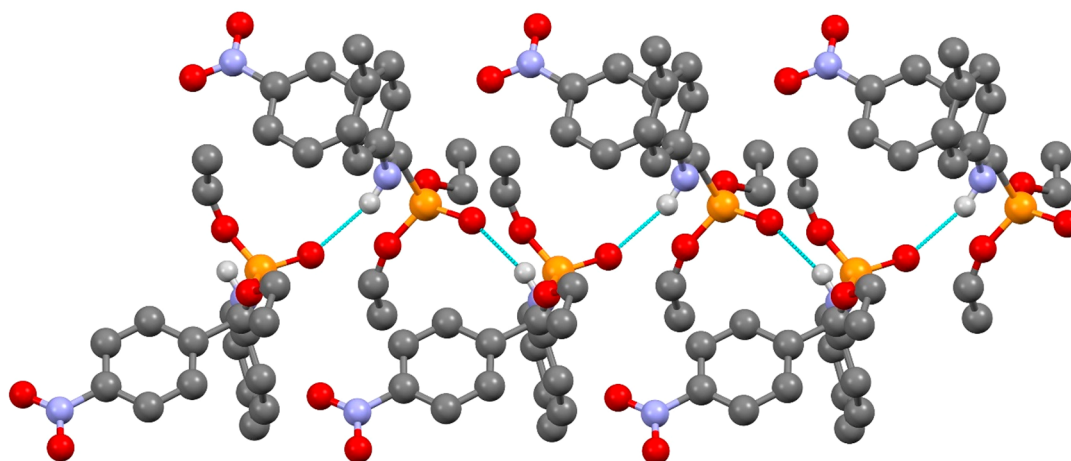
**Figure 6.** Crystal packing of **1** (top) viewed along the crystallographic *bc*-plane and of **11** (bottom) viewed along the crystallographic *ac*-plane.  $H_{CH}$  have been omitted for the sake of clarity.

Commercially available milling media based on zirconium oxide have never been explored as heterogeneous and “recyclable catalysts” in any metal-mediated mechanochemical transformation described in the literature.<sup>60</sup> They outperform stainless steel jars and complement the previous findings making use of manufactured on purpose copper-,<sup>49,50</sup> nickel-<sup>51</sup> and palladium-milling<sup>52</sup> media to catalyze *click* [3 + 2], [2 + 2 + 2] cycloaddition, and Suzuki–Miyaura reactions, respectively.

To explain the hypothesized role played by the Zr-based milling media, the mechanochemical Pudovik reaction (method B, Scheme 2) was investigated using as starting materials *E*-imines having different electronic properties. We speculated that the addition of diethyl phosphite to the C=N bond would be successful with electron-rich imines, where the increased density on the nitrogen atom may favor the coordination with the ZrO<sub>2</sub> Lewis acid.

Unexpectedly, step 2 of Pudovik reaction was unsuccessful when diethyl phosphite was milled with both electron-poor benzylidene(4-chlorophenyl)amine *E*-1 (from entry 1a) or electron-rich benzylidene(naphthalen-2-yl)amine *E*-2 (from entry 1b); in the optimized conditions already disclosed (milling time was 4 h in this case) only traces of corresponding  $\alpha$ -aminophosphonates were detected in the <sup>1</sup>H NMR of the crude, the main product being always the unreacted starting *E*-imines, with no *E/Z* isomerization reaction detected even in traces.

These preliminary findings shed light on the differences between solution vs mechanochemical methods to access  $\alpha$ -aminophosphonates.<sup>60</sup> In solution, their preparation is preferably carried out by Pudovik method, involving a Lewis acid as catalysts, to promote the addition of diethyl phosphite to C=N bond. However, the use of Lewis catalysts is not always effective for solution-based Kabachnik–Field process. Even if this domino reaction involves the formation of an intermediate imine, the Lewis acid can be deactivated by nitrogen-containing compounds (the starting amine) or by the presence of water,<sup>22</sup> formed *in situ* during the reaction process. This is particularly true especially for moisture-sensitive catalysts (e.g. ZrCl<sub>4</sub><sup>57</sup>), even if dehydrating agents or water-stable catalysts such as rare earth metal triflates can be used as alternatives.



**Figure 7.** “Catemer” type hydrogen bonded network in crystalline diethyl(((4-methylphenyl)amino)(4-nitrophenyl)methyl)phosphonate KANWEE.<sup>89</sup>  $H_{CH}$  have been omitted for the sake of clarity.



These limitations impact negatively on the use of KF-3CR in solution, limiting the choice of possible catalysts and reducing the environmental footprint of the reaction [e.g. generating more (toxic) waste]. These problems are overcome when performing the KF-3CR by mechanochemistry, resulting fully effective in our conditions.

Therefore, ball-milling the reactants in ZrO<sub>2</sub> jars may represent a sustainable alternative to classic heterogeneous catalysis making use of Lewis acids in solution (water-sensitive or not). Additionally, in the case of a possible metal-mediated process involving the milling media, the jar can be considered as a recyclable catalyst, with the advantage of not being responsible for metal-waste production, expanding the reactivity windows for heterogeneous KF-3CR. In this regard, zirconium-<sup>58</sup> or other metal-mediated synthesis of imine cannot be excluded, the process possibly occurring on the jar/balls surface.

Among the advantages, zirconium oxide milling media benefit of the advantages of Zr(IV) derivatives, displaying a limited redox character,<sup>61</sup> low toxicity,<sup>62</sup> and acting as adhesion promoters in the presence of oxygenated species (including carbonyl groups).

**Synthesis of a Library of  $\alpha$ -Aminophosphonate Derivatives.** Once the optimized mechanochemical conditions were disclosed for KF-3CR method (Table 1, entry 4), a library of  $\alpha$ -aminophosphonate derivatives 1–16 was prepared. The reaction were fully selective and excellent isolated yields were obtained whatever were the arylamine/arylaldehyde/P-nucleophile combination [P-nucleophiles: P(O)H(OEt)<sub>2</sub>, P(O)H(O<sup>i</sup>Pr)<sub>2</sub>, and P(O)H(Ph)<sub>2</sub>] (Scheme 5).<sup>63</sup> The  $\alpha$ -aminophosphonates 1–11 and  $\alpha$ -aminophosphine oxides 12–16 herein prepared present N-, C-, and P-modifications, and they were easily recovered by precipitation in water/filtration as previously described. The process was characterized by the absence of any side reaction (Scheme 3), including the Abramov pathway to  $\alpha$ -hydroxyphosphonates or their rearrangement to phosphates and their amine-promoted decomposition. This greatly simplified the workup procedures, making the mechanochemical Kabachnik–Fields reaction particularly straightforward compared to solution-based procedures.

Mechanochemical activation was particularly outperforming to prepare  $\alpha$ -aminophosphine oxides 12–16. Generally speaking, the preparation of this class of compounds is usually poorly investigated in solution. Their preparation usually requires the use of a large excess of amine, high temperature and long reaction times,<sup>21</sup> with a negative consequence also on the stability of diphenylphosphine oxide reactants, generating the corresponding oxidized diphenylphosphinic acid by-product. In this regard, a chromatographic purification of the final  $\alpha$ -aminophosphine oxides is required, detrimental from the point of view of the ecological footprint of the intrinsically sustainable process.

Worthy of note is that the reactivity of the KF-3CR by mechanochemistry was influenced by the nature of the P-nucleophile used. As a general trend, the preparation of diethyl esters of  $\alpha$ -aminophosphonates required 4 h milling in the optimized reaction and process conditions (see the Supporting Information), while 6 h milling was needed to achieve full conversion of the starting reagents (e.g. compounds 1 and 2 vs compounds 11 and 10, respectively), when increasing the branching at the alkyl chain of the P-nucleophile [P-

nucleophiles: P(O)H(OEt)<sub>2</sub> or P(O)H(Ph)<sub>2</sub> vs P(O)H(O<sup>i</sup>Pr)<sub>2</sub>].

The same trend was also verified in the case of  $\alpha$ -aminophosphine oxides 12 and 13, prepared faster (in a 4 h reaction) compared to their respective di-*iso*-propyl counterparts 11 and 10 (requiring 6 h and less energetic conditions).<sup>64</sup>

On the basis of this finding, by grouping the  $\alpha$ -aminophosphonate derivatives in the series having the same combination aldehyde/amine, but different P-nucleophiles (e.g. compounds in group I 1, 11–12; group II 2, 10, 13; group III 6 and 15; group IV 7 and 16) a reactivity trend can be disclosed, independently on the physical state of each reactant (liquid or low melting solid). The reactivity and reaction kinetics decreased in the order P(O)H(Ph)<sub>2</sub> > P(O)H(OEt)<sub>2</sub> > P(O)H(O<sup>i</sup>Pr)<sub>2</sub>. Steric hindrance was ruled out as the possible reason for slower kinetics observed when increasing the branching at the alkyl, during the addition reaction of the P-nucleophile to the C=N bond, mechanochemical activation being able to challenge the reactivity of hindered substrates.<sup>11,65</sup>

A possible explanation could rely on the slower kinetic of tautomerization of P(O)H(O<sup>i</sup>Pr)<sub>2</sub> compared to P(O)H(OEt)<sub>2</sub>, in the absence of a suitable proton carrier (usually the solvent). DFT studies demonstrated that the intramolecular proton transfer pathway is disfavored for high activation barriers.<sup>66,67</sup> In this regard, the tautomeric equilibrium can possibly occur on the jar surface, mediated by the ZrO<sub>2</sub> or trace metals composing the milling media. These results clearly strengthen the previous observations, by confirming that the reactivity trend for KF-3CR by mechanochemistry is quite different from solution-based procedures, mainly favoring the Pudovik method to prepare  $\alpha$ -aminophosphonate derivatives. Additionally, with the solubility problems ruled out by mechanochemistry, the imine formation is not the rate-determining step for KF-3CR during milling. Thus, the reactivity trends exclusively depend on the intrinsic nucleophilic character of the phosphorus derivatives (and their respective tautomerization kinetics) and their resistance to hydrolysis. Because diphenylphosphine oxide P(O)H(Ph)<sub>2</sub> is not sensitive to hydrolysis, a stoichiometric amount can be used compared to P(O)H(OEt)<sub>2</sub> and P(O)H(O<sup>i</sup>Pr)<sub>2</sub> (1.5 equiv were required).

The preparation of  $\alpha$ -aminophosphonates 8 and 9, involving the electron-rich 4-*N,N*-dimethylbenzaldehyde as starting material, occurred by a one-pot/two-step Pudovik method; however, the preparation of the corresponding  $\alpha$ -aminophosphonates from electron-poor 4-nitrobenzaldehyde proved to be unsuccessful. These opposite outcomes suggested that the electronic nature of the intermediate imine can drive a switch of reactivity. Indeed, the increased electron density on the nitrogen atom of the imine may favor the coordination with the Lewis acid (e.g. ZrO<sub>2</sub>) promoting the addition of the P-nucleophile across the C=N bond of the transient imine, while the reaction failed with electron poor substrates (Scheme 4).

Additional results supporting the experimental evidence already disclosed regarding the postulated influence of surface-mediated process by alternative Zr-sources or other metals was obtained by repeating the reactions in stainless steel jars, in the same reaction conditions (Table 1 entry 4 and the Supporting Information). The reactions were substrate dependent and a residual amount of aldehyde was always detected by <sup>1</sup>H NMR analyses of the crude mixtures.

Another set of experiments was performed to demonstrate the beneficial effect played by mechanochemical activation for KF-3CR in comparison with solution-based procedures requiring thermal activation. It is generally demonstrated that under thermal heating the reaction is very slow or did not proceed at all, without a catalyst. The only exceptions relies on solvent-free procedures under microwaves<sup>24,68</sup> (heating up to 120 °C) or activated by indirect sonication<sup>34</sup> (with no control of the temperature). Therefore, the preparation of  $\alpha$ -amino-phosphonate **2** and  $\alpha$ -aminophosphine oxide **13** (Tables S1 and S2)<sup>64</sup> was investigated in a sealed pyrex tube in solution or neat, at room temperature or upon heating up to 70 °C. Even if good conversions were achieved in some cases after 5 h (in THF, CH<sub>3</sub>CN, and in neat conditions), the conversion of the starting reactants was never complete, residual imine was still present, and postreactional treatments were always necessary (liquid–liquid extraction and purification by chromatography), negatively impacting the ecological footprint of the process.

These results clearly demonstrated that thermal activation alone was not enough for achieving full conversions and high yields and that alternative energy inputs based on tribochemical processes, such as ultrasound<sup>34,69</sup> and mechanochemistry, were more effective and solved the drawbacks experienced upon thermal activation. They have in common similar activation effects,<sup>70,71</sup> providing unusual reaction conditions and prohibitive activation barriers compared with the traditional thermal activation methods.

The ball-milling procedure for the Kabachnik–Fields reaction outperformed other solution procedures: (a) avoiding the use of additives and hazardous solvents, a large excess of phosphorus nucleophile and stoichiometric amounts of (toxic and nonrecyclable) catalysts (*reagent and solvent economy*); (b) not requiring chromatographic purifications, avoiding a large amount of (toxic) waste generally associated with byproduct formation, workup, and product isolation, and not requiring chromatographic purifications; (c) avoiding any heating (*energy economy*); (d) simplifying the catalytic system (the jar can be used ideally for infinite reactions) making also thermally reluctant reactions possible; (e) providing high selectivity and clean reaction profiles, reducing the environmental footprint of the process (*waste economy*); (f) reducing reaction times (*time economy*); and (g) allowing access to selective and high yield  $\alpha$ -aminophosphonate derivatives by KF-3CR, usually low yielding in solution, and preferably prepared by the stepwise two-component Pudovik reaction. Therefore, KF-3CR in solution, usually considered not selective or low yielding compared to the preferable stepwise two-component process (Pudovik reaction),<sup>17</sup> is particularly effective under milling conditions.

**KF-3CR Using Aliphatic Amines.** The preparation of  $\alpha$ -aminophosphonates from aliphatic amines deserves a separate discussion. Actually, the mechanochemical KF-3CR developed from aromatic amines seems to be not as effective when cyclohexylamine was used. The KF-3CR to  $\alpha$ -aminophosphonate **17** in the conditions previously developed (Table 1, entry 4) was low yielding (25–30% conversion) and not selective (Scheme 5). <sup>1</sup>H NMR and <sup>31</sup>P NMR analyses of the crude indicated that the  $\alpha$ -aminophosphonate **17** was formed, but the Abramov product  $\alpha$ -hydroxyphosphonate product was the major compound ( $\alpha$ -NH<sub>2</sub>/ $\alpha$ -OH ratio 0.6:1), with still 14% residual amount of imine (Table 2, entry 1). The preparation of diethyl  $\alpha$ -cyclohexylamino-4-benzylphosphonate **17** was also carried out by one-pot/two-step

Pudovik reaction; conditions were also tested to access diethyl  $\alpha$ -cyclohexylamino-4-benzylphosphonate **17** (Table 2, entry 2).

<sup>1</sup>H NMR and GC/MS analyses confirmed that the formation of imine (*step 1*) is the bottleneck of this synthesis (30% conversion after 1 h milling at 600 rpm). After the addition of diethyl phosphite (*step 2*), the compounds were milled for further 4 h in the same conditions. Besides, the reaction was not selective and a mixture composed by 64% in favor of  $\alpha$ -hydroxyphosphonate was formed ( $\alpha$ -OH/ $\alpha$ -NH<sub>2</sub> ratio was 1.81:1), due to the competitive P-addition of diethyl phosphite to the C=O group of the residual benzaldehyde, instead of the C=N group of the newly formed intermediate imine.

Therefore, for both mechanochemically activated KF-3CR and Pudovik reaction, the results suggest that slow kinetics characterize the formation of the imine when cyclohexylamine and benzaldehyde are used, favoring the competitive Abramov side-reaction. Worthy of note, when aromatic amine was used instead of aliphatic cyclohexyl amine (*e.g.*  $\alpha$ -aminophosphonate **3** vs  $\alpha$ -aminophosphonate **17**), the  $\alpha$ -hydroxyphosphonate was never observed, even in traces (Scheme 5). This is in perfect agreement with the outcomes observed in solution, where the “switch” of the selectivity depended on the ease of imine formation.

To further confirm this trend for the mechanically activated KF-3CR, cyclohexylamine was reacted with two aldehydes having electron withdrawing substituents (*e.g.* 4-nitrobenzaldehyde and 4-chlorobenzaldehyde) in the presence of diethyl phosphite (Table 2, entries 3 and 4). The mixture was milled during 4 h at 600 rpm in ZrO<sub>2</sub> grinding media, as previously described (Table 1, entry 4). When using the more electrophilic 4-nitrobenzaldehyde, the formation of 4-nitrobenzylidene(cyclohexyl)amine and the subsequent addition of the P-nucleophile went to completion; however the corresponding  $\alpha$ -aminophosphonate was formed together with 27% of  $\alpha$ -hydroxyphosphonate, as assessed by <sup>1</sup>H NMR analyses of the crude (Table 2, entry 3). In the case of 4-chlorobenzaldehyde, this trend was also confirmed (Table 2, entry 4); however, a residual 30% of imine was still present in the crude after 4 h milling. These data clearly show that with cyclohexylamine, the rate for imine formation depended on the nature of carbonyl compound, with faster kinetics for electron-withdrawing substituents. This influenced also the reaction pathway driving the selectivity switch between KF-3CR vs Abramov reaction, under a preferred thermodynamic control toward the formation of the  $\alpha$ -aminophosphonate in the presence of electrophilic aldehydes. In comparison, with aromatic amines, the mechanochemical activation drives the selectivity exclusively toward the “imine pathway”, with no formation of  $\alpha$ -hydroxyphosphonate, whatever is the combination amine/aldehyde involved (Scheme 5).

Several other process conditions in a vibratory ball-mill operating at 30 Hz were explored for accessing diethyl  $\alpha$ -cyclohexylamino-benzylphosphonate **17** (*e.g.* Teflon or PMMA jars, stainless steel or ZrO<sub>2</sub> balls and use of additives). As a general trend, <sup>1</sup>H NMR analyses of the crude revealed, in all cases, that (a) the conversion of benzylidene(cyclohexyl)amine was incomplete even after 18 h milling and (b) the Abramov reaction pathway leading to the corresponding diethyl-[hydroxy(phenyl)methyl]phosphonate was always favored.

Taking into account the reversibility of Abramov reaction in solution,<sup>6</sup> the preparation of  $\alpha$ -[cyclohexylamino-(phenyl)-

methyl]phosphonate **17** was attempted by milling diethyl-[hydroxy(phenyl)methyl]phosphonate with a 2-fold excess of cyclohexylamine. The reaction was carried out at 30 Hz for 4.5 h in a Teflon jar (14 mL) with 1 zirconium oxide ball (8 mm diameter). However, in these conditions, no reaction occurred, ruling out that Abramov reaction could also lead to Kabachnik–Fields product **17**.

**Investigation of the KF-3CR by *in Situ* Raman Spectroscopy.** The study was also focused on the investigation of the KF-3CR mechanism occurring during mechanochemical activation. The reaction was monitored by *in situ* Raman spectroscopy.<sup>41</sup>

Attempts to perform reaction monitoring by *in situ* Raman spectroscopy were hindered by high luminescence of almost all reaction mixtures which either obscured the Raman scattering signal from the sample or saturated the detector, even at low incident laser power, rendering any measurements impossible. *In situ* reaction monitoring was successful only for experiments where *N,N*-dimethylaminobenzaldehyde (dmab) and *p*-chloroaniline (pClan), both solids at ambient conditions, were milled in the presence of diethyl phosphite—a reaction yielding the  $\alpha$ -aminophosphonate **9**. Milling of the three reactants usually resulted in sticky reaction mixtures leading to uneven mixing and possibly a complete loss of the Raman scattering signal if the mixture got stuck in the corner of the PMMA reaction vessel. Therefore, we have attempted using NaCl as an inactive additive to keep the mixture in the form of a free-flowing powder. Even if the conversion of the reactants was not complete, Raman spectra could be collected (Figure 1). The *in situ* monitoring, with the time resolution of 10 s, revealed rapid loss (within first 3–4 spectra corresponding to ca. 30–40 s of milling) of the C=O stretching band of the dmab at 1659 cm<sup>-1</sup> and a subsequent slower formation of the corresponding Schiff base, via an intermediate. The Schiff base results from the reaction of the dmab and pClan and is evidenced by the emergence of a set of bands positioned around 1600 cm<sup>-1</sup> and a band at 983 cm<sup>-1</sup> (Figure 1). Subsequent *ex situ* <sup>1</sup>H NMR analysis of the crude reaction mixture confirmed that the conversion of the reactants and the Schiff base to the target  $\alpha$ -aminophosphonate **9** was not complete. The conversions were determined by comparing the <sup>1</sup>H NMR relative ratio of the integrals associated with the signals of (a) the CH=O proton of the starting dmab (singlet at 9.73 ppm in CDCl<sub>3</sub>, 24% of the crude mixture), (b) the CH=N proton (singlet at 8.27 ppm, 35% of the crude mixture) of the corresponding Schiff base, and (c) the P–CH–NH proton (doublet at 4.58 ppm, 41% of the crude mixture) in the  $\alpha$ -aminophosphonate **9**.

However, from the *in situ* Raman spectra, the presence of the  $\alpha$ -aminophosphonate **9** could not be evidenced and only the Schiff base was observed. This is likely due to its dominant contribution to Raman scattering where the scattering signal from other species is of significantly lower intensity. To verify that the *in situ* collected final Raman spectrum for the preparation of  $\alpha$ -aminophosphonate **9** corresponds to the Schiff base spectrum, we have conducted *in situ* reaction monitoring of the preparation of the pure Schiff base (Figure 2). Virtually identical spectra in these two experiments confirm the previous assumption but, importantly, also that the Schiff base is formed as an intermediate in the KF-3CR reaction (Figure 3).

Noteworthy, in the milling conditions used, the *in situ* Raman spectra of the KF-3CR reaction showed the presence of

a stable Schiff base, which translates in a very slow Pudovik reaction or its full inhibition. This is in accordance with the observation that stainless steel milling media prevented the KF-3CR product formation. Observation of the product in our case by *ex situ* NMR analysis could have been the result of the reaction advancing after cessation of milling and before the *ex situ* analysis, upon aging the sample overnight, or slowly proceeding in the NMR tube.

Interestingly, reaction toward Schiff base formation during the KF-3CR is extremely fast as evidenced from the loss of the aldehyde band within 2 min of milling. However, in the absence of diethyl phosphite (*i.e.* method B, Scheme 2 for the first step of the Pudovik reaction targeting the Schiff base preparation), the conversion of the starting dmab is 2 orders of magnitude slower, with the aldehyde C=O stretching vanishing after 2 h of milling. This may suggest a catalytic role played by the diethyl phosphite for the Schiff base formation. This investigation was not pursued further as it lays outside the scope of this work.

The KF-3CR leading to the  $\alpha$ -aminophosphonate **9** can nevertheless be driven to completion carrying out the reaction in a Teflon jar (instead of a PMMA jar) and milling the mixture during 16 h, without the use of milling additives. Unfortunately, the Raman *in situ* monitoring can be carried out only in translucent PMMA vessels. White Teflon does not permit the incident Raman laser light to penetrate the reaction vessel walls. Worthy of note is the increased reactivity observed when stainless steel balls were replaced by one ZrO<sub>2</sub> ball (8 mm diameter, weight of the ball *m* = 1.6 g). In this case, the reaction went to completion after 5 h, confirming that the milling media acted as the necessary Zr source to promote efficiently the Pudovik reaction.

**Kinetics for KF-3CR.** Starting from the Raman data collected *in situ* for the preparation of the  $\alpha$ -aminophosphonate **9**, the kinetic behavior under mechanochemical processing for the KF-3CR was also disclosed. Quantitative analysis of Raman spectra allowed evaluating changes in mole fractions of reactants and the Schiff base product. The KF-3CR product was not observed in the *in situ* Raman spectra being obscured by the dominant scattering contribution from the Schiff base.

The results are shown in Figure 4, where the mole fractions of reactants, intermediate, and the Schiff base are plotted as a function of time. Reactants undergo an immediate and relatively fast monotonic decrease associated with a corresponding increase of the intermediate.

Although very small amounts of Schiff base are detected since the very beginning of the mechanical processing, it is only after about 80 s that its mole fraction starts increasing. After about 300 s, the mole fraction of Schiff base reaches the value of about 0.9.

The kinetics behavior has been tentatively rationalized using a simplified kinetic model. Described in detail in a recent publication,<sup>42</sup> the model accounts for the statistical nature of the mechanical processing of powder by ball-milling. Specifically, it combines the statistical nature with the chemical conversion activated by individual impacts, thus providing a set of kinetic equations that can be used to best-fit the experimental points. In the present case, the reactant data set can be satisfactorily best-fitted by the simple exponential eq 1:

$$\alpha_t = \exp(-kt) \quad (1)$$



where  $\alpha_r$  is the volume fraction of reactants,  $k$  is the apparent reaction rate and  $t$  is time. Specifically,  $k$  measures the volume fraction of powder that is processed effectively per unit time.<sup>42</sup> The intermediate volume fraction can be described by the eq 2:

$$\alpha_i = \left[ kt + \frac{(kt)^2}{2!} + \frac{(kt)^3}{3!} + \frac{(kt)^4}{4!} + \frac{(kt)^5}{5!} + \frac{(kt)^6}{6!} + \frac{(kt)^7}{7!} \right] \exp(-kt) \quad (2)$$

while the Schiff base product volume fraction can be expressed as

$$\alpha_p = 1 - \alpha_r - \alpha_i \quad (3)$$

In the absence of more accurate information on the microscopic processes taking place on the microscopic scale during individual impacts, the interpretation of experimental data can be only phenomenological. In this respect, eqs 1 and 3 indicate that at least one impact is needed to activate the transformation of reactants into the intermediate, whereas eight impacts are required to form the Schiff base. Accordingly, the intermediate exhibits a considerable persistence under the mechanical processing conditions compared with reactants.

To a first approximation, the kinetic data can be best-fit using a single value of the apparent rate constant  $k$ , equal to about 0.0343 s<sup>-1</sup>. The use of a single  $k$  represents the best choice under the present experimental circumstances, which do not allow obtaining independent information on local processes occurring on the molecular scale. Even so, the  $k$  value allows estimating the amount of reactants and intermediates involved in effective compression events during individual impacts.

Taking into account that the total mass of powders inside the reactor is approximately 680 mg, the amount of material effectively processed per unit time is equal to about 23 mg. If we assume that the frequency of impacts is approximately 120 Hz, which is reasonable based on the use of a single ball and a reactor swing frequency of 30 Hz, we can expect that the mass of material compressed critically during each impact is around 0.2 mg.

Therefore, our experimental findings and the interpretation we give based on the kinetics analysis confirm that only a very small fraction of the material inside the reactor is effectively processed during individual impacts. Discovering what happens to powders on the microscopic scale remains one of the most ambitious objectives in the field of mechanochemistry and a necessary step to further progress on the way to practical application of mechanochemical methods.

**Solid-State Characterization of  $\alpha$ -Aryl- $\alpha$ -aminophosphonate 1 and 11.** Among the compounds reported in this work compounds 1 and 11 (Scheme 5) have been chosen as representative examples of the *diethylphosphonate* and of the *diisopropylphosphonate* groups to illustrate the principal molecular and crystal structure features as determined by single-crystal X-ray diffraction.<sup>64</sup> Correspondence between the structures of the compounds in the bulk materials resulting from the mechanosyntheses and those of the single crystals obtained from solution was verified by comparing<sup>64</sup> experimental powder diffraction patterns measured on polycrystalline samples of 1 and 11 with the diffractograms calculated on

the basis of the single crystal structures described in the following.

The molecular diagrams together with the labeling schemes are shown in Figure 5. 1 and 11 share the fundamental structural unit of  $\alpha$ -aryl- $\alpha$ -aminophosphonates and crystallize as racemic crystals with molecules organized in centrosymmetric hydrogen bonded dimers (vide infra) in the space groups  $P2_1/c$  and in  $\bar{P}1$  for 1 and 11, respectively.

The hydrogen bonded rings formed by pairs of molecules in 1 and 11 can be described in graph set notation<sup>77</sup> as  ${}^2_2R(10)$ , viz. ten member rings with two hydrogen bonding N–H donors and two acceptor P=O groups. There is a noticeable difference in hydrogen bond length within the two ring systems with  $N_{NH} \cdots O_{PO}$  of 2.943(5) and of 3.116(6) Å in 1 and 11, respectively. Such a difference can be ascribed to the larger steric demand of the isopropyl group in 11 with respect to the small ethyl groups in 1 hindering a closer approach in the former ring. A similar effect has been observed in a number of other cases<sup>78–83</sup> and is substantiated by the comparison with other diethyl and diisopropyl aminophosphonates forming  ${}^2_2R(10)$  rings extracted from the CSD<sup>84</sup> and shown in Table 3.

It is interesting to note that the crystal structures of 1 and 11 (see Figure 6 for views of the packings) although both compounds have been prepared by mechanochemical methods as described herein present the same hydrogen bonded dimers as observed in many related compounds obtained by more conventional methods. For example, a similar hydrogen bonded ring is present in compound 3 whose structure had been previously determined by others (DEABPH<sup>78</sup>) and obtained first by a conventional solution method<sup>85,86</sup> and later via an unconventional procedure (MW)<sup>87</sup> and also by us (see Scheme 5). As a matter of fact, all compounds listed in Table 3 share with 1 and 11 the same fundamental  ${}^2_2R(10)$  hydrogen bonding motif.

While this is not surprising *per se*, it is interesting to speculate on the fact that different processes, whether via solution or mechanochemistry, terminate with the same molecular recognition outcome.

This consideration lends further support to the idea that molecules, even complex molecules such as those discussed herein, have great mobility also in solid–solid or solid–liquid mixtures and that the crystal nucleation stage follows exactly the same selection rules as in solution, leading in all these cases to crystals built around the same supramolecular dimers.

Finally, one may wonder why, in analogy with the crystal structures of carboxylic acids, the alternative “catemer” type arrangement, *i.e.* the extended one-dimensional hydrogen bonded polymer,<sup>88</sup> with no ring formation is not adopted in crystals of the aminophosphonates discussed here (Figure 7).

The alternative “catemer” type hydrogen bonded polymer has been observed, for example, in the crystal of the phosphonate diethyl(((4-methylphenyl)amino)(4-nitrophenyl)methyl)phosphonate (KANWEE<sup>89</sup>); see Figure 7.

The reason for the structural preference is not easily rationalized, although one may observe that the catemer type packing is not compatible with the formation of centrosymmetric molecular pairs which, as discussed above, are likely to aggregate prior to crystal nucleation stage, whether in solution or in the condensed phase. The existence of polymorphic modifications of the crystals of the species discussed herein cannot be ruled out and deserves an *ad hoc* investigation.

## CONCLUSIONS

KF-3CR reaction, already synthetically powerful, become operationally simple, fully selective, and sustainable when milling conditions were used. It was demonstrated that the reaction was promoted by surface-mediated interactions of the reactants and intermediates involving the zirconium oxide jar (and balls). The mechanochemical procedure allowed a fully selective transformation (byproducts are avoided) and the final  $\alpha$ -aminophosphonates were easily recovered by precipitation in water and not a drop of organic solvent was used for both synthesis and workup. Additionally, the formation of phosphorus–carbon bonds by Kabachnik–Fields reaction under ball-milling conditions outperforms that of solution-based procedures and allowed straightforward access to  $\alpha$ -aminophosphonates and less common  $\alpha$ -aminophosphine oxides having structural diversity and complexity. The preparation of compounds potentially endowed with biological activities, the investigation of the reaction mechanisms by *in situ* Raman spectroscopy,<sup>90</sup> and the study of the kinetics of the process,<sup>42,43</sup> contribute to the advancement of a recent area of investigation referred to as *medicinal mechanochemistry*.<sup>16,91</sup> In this regard, in view of the potential pharmaceutical applications of new active compounds, the evergreen topic of solid-state characterization merged with mechanochemical procedures for their preparation is more than ever of actuality, in view of the discovery of novel pharmaceutical polymorphs.<sup>92</sup>

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.0c05744>.

Experimental procedures and <sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P spectral data of compounds 1–17. Structural and PXRD data for compounds 1 and 11 (PDF)

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## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

E.C. expresses her gratitude towards BetaInnov ([www.beta-innov.com](http://www.beta-innov.com)) for providing the planetary milling equipment for conducting the research project. C.F. is grateful to the E.U. (Erasmus Program, Università degli Studi di Torino, Italy) for the fellowship. E.C. is grateful to Gladys Da Conceição (Fritsch, France) for providing detailed technical information on the milling media and the image of the planetary mill used for the experiments. A.P. is grateful to MIUR (Italy, PRIN project: Multi-Functional polyMER cOMposites based on groWn matERials, no. 2017B7MMJ5\_001). D.B., C.F., and O.S. are grateful to Dr. Katia Rubini (University of Bologna, Italy) for the assistance with the DSC measurements. This article is based upon work from COST Action CA18112,<sup>93,94</sup> supported by COST (European Cooperation in Science and Technology).<sup>95</sup> The manuscript was written during the worldwide lockdown due to COVID-19 pandemic disease.

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- (63) Isolated yields are given for compounds 1–17. For further experimental details, please refer to the Supporting Information. The conversion in favor of compound 18 was determined by <sup>31</sup>P and <sup>1</sup>H NMR (method A 24%, method B 30%). Dialkyl phosphites are well known as powerful alkylating agents. The reaction generally proceeds through a S<sub>N</sub>2 mechanism, and in this series, dimethyl phosphite is the most reactive one. Please see as non-exclusive example: Kundu, S. K.; Mitra, K.; Majee, A. Dialkyl phosphite as a highly selective mono-N-alkylating agent using indium triflate under microwave irradiation. *RSC Adv.* **2013**, *3*, 8649–8651. The mindset of this work is to provide an ecofriendly approach to access  $\alpha$ -aminophosphonates, as an alternative to solution-based procedures, applying the highest number of the 12 Green Chemistry Principles<sup>5</sup> as possible. The use of dimethyl phosphite violates principles 3 (less hazardous chemical synthesis), 4 (design safer chemicals), and 12 (inherently safer chemistry for accident prevention), but its reactivity fully compares with diethyl phosphite, preferable for safety reasons. Dimethyl phosphite is a substance classified as carcinogenic, mutagenic, or toxic for reproduction (CMR), while diethyl phosphite is not. For more information, please refer to the safety data sheet of each compound.
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